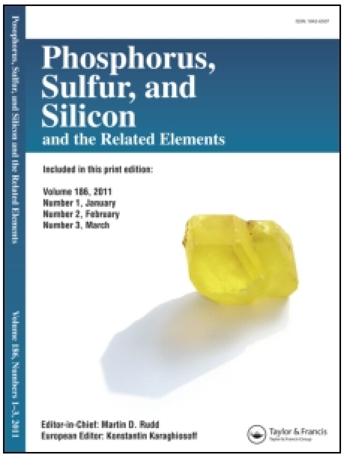

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New Free Radical and Photochemical Routes to Phosphonate Oligonucleotide Precursors

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New photochemical and free radical reactions are applied to the synthesis of dinucleoside 2-phenylallylphosphonates and prenucleotide model vinylphosphonate systems.

Keywords: oligonucleotides; photochemistry; free radicals; phosphonates

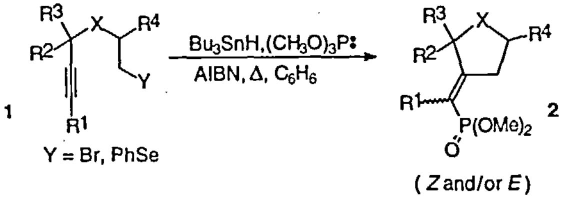
INTRODUCTION

Oligonucleotides, suitably modified in the vicinity of the phosphorus backbone to impart nuclease resistance, are the key molecules in the antisense approach to antiviral and antitumor therapy.[1] We report here applications of two new approaches to the preparation of subunits for incorporation into deoxyribose-based oligonucleotides.

RESULTS

The first takes advantage of: 1) the rapid 5-exo digonal cyclization of 5-hexynyl and 3-oxa-5-hexynyl free radicals to generate vinyl radical intermediates;[2] and 2) the known increased reactivity towards trialkyl phosphites of carbon-centered radicals whose SOMO's possess considerable *s* character.[3] The overall reaction is given by the conversion of **1** to **2** (X = CH_2 or O). Mechanistically, this process is presumed to proceed through a cyclic vinyl radical that is trapped by reaction with trimethyl phosphite.

Product **2**, with appropriate substituents R^1-R^4, becomes a deoxy ribonucleoside-based phosphonate, or its carbocyclic analog, that with appropriate

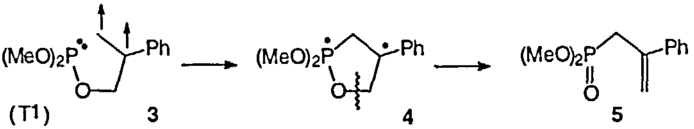


functionalization at the 3'- and 5'-termini can be incorporated into an oligonucleotide chain. The vinyl linkage will not be susceptible to hydrolysis by nucleases and thus will impart stability to an oligonucleotide backbone in antisense applications. The C=C bond at the 3'-position will be resistant to rotation. Therefore, the stability of oligonucleotide duplexes and triplexes which incorporate subunit **2** will vary with C=C geometry. The π electrons of the C=C moiety may impart properties that make this linkage not only isosteric with 3'-CHO but also more nearly isoelectronic than a CH$_2$-P bond at C-3'.

Under standard thermal AIBN-initiated, Bu$_3$SnH-mediated radical cyclization conditions, **1** was converted to **2** in 75-90% isolated yields. Typical substituent patterns included combinations of: R^1 = H, Me, isoPr, *tert*-Bu, Ph; R^2 = H, Me; R^3 =BnOCH$_2$, Ph, Me; R^4 = EtO, Ph.

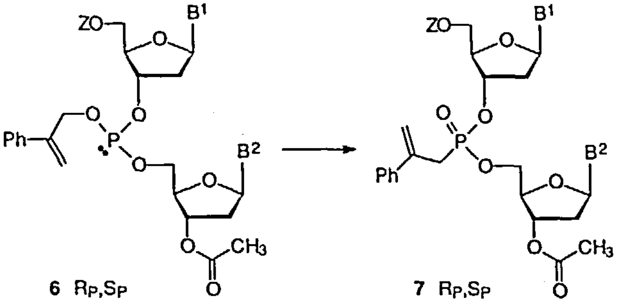
For X = CH$_2$, R^1 the series of substituents given above, and R^2 = R^3 = R^4 = H, good yields of product **2** were obtained except for R^1 = *tert*-Bu. *Z* vs *E* stereoselectivity as a function of substituents R^1-R^4 was observed. In general terms, with X = O and R^4 = H or a substituent, approximately equal quantities of *E* and *Z* forms of **2** resulted. With R^2 or R^3 a single non-hydrogen substituent, a bias towards (*E*)-**2** was noted. Appropriate disubstitution (R^2 = R^3 = Me) gave rise to (*E*)-**2** exclusively. Details of these results, our understanding of them, along with experiments to define the role of kinetic versus thermodynamic control of these processes, will be reported elsewhere.

The second approach aimed towards the introduction of new phosphorus



functionality into oligonucleotide chains utilizes a novel photoprocess devised in this lab, the triplet-sensitized photorearrangements of 2-phenylallyl phosphites.[4] As shown in the sequence 3 → 4 → 5, triplet 5, a 1,2-biradical-like excited state of dimethyl 2-phenylallyl phosphite, cyclizes to the phosphoranyl 1,3-biradical 4 that then undergoes intersystem crossing and β scission to yield 2-phenylallylphosphonate 5.

Application to dinucleoside 2-phenylallyl phosphites is illustrated by the conversion of 6 to 7. With Z = TBDMS the base combinations examined were: $B^1 = B^2 = T$; $B^1 = A^{Bz}$, $B^2 = T$; $B^1 = C^{Bz}$, $B^2 = T$, and for the case Z = DMTr, $B^1 = B^2 = T$. Isolated phosphonate yields of 60-70% were achieved in photoreactions easily carried out by triphenylene-sensitized reactions of acetonitrile solutions of phosphite 6 irradiated through Pyrex. In the two cases attempted so far, the R_P and S_P forms were easily separated. The 2-phenylallylphosphonate moiety provides a group that can be readily further functionalized. Indeed, MCPBA oxidation of the individual R_P or S_P diastereomers of phosphonate 7, for the case $B^1 = B^2 = T$, gave high yields of readily separated diastereomeric pairs of styrene oxides.



CONCLUSIONS

A new radical reaction sequence has been employed to prepare cyclic methylene phosphonates (phosphonomethylenes) in model systems that appear suitable for application to the synthesis of analogous nucleoside-based phosphonates. Triplet-sensitized photorearrangements of dinucleoside 2-phenylallyl phosphites yield the corresponding phosphonates with functionality amenable to further chemical modification. Phosphonates derived from both approaches appear to be good candidates for incorporation into oligonucleotides to impart unusual chemical and/or physical properties.

Acknowledgments

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[3] K.P. Dockery, W.G. Bentrude, *J. Am. Chem. Soc.* **119,** 1388–1399 (1997).

[4] See for example, W.G. Bentrude, K.P. Dockery, S. Ganapathy, S.-G. Lee, M. Tabet, Y.-W. Wu, R.T. Cambron, J.M. Harris, *J. Am. Chem. Soc.* **118,** 6192–6201 (1996). Y. Huang, W.G. Bentrude, *Tetrahedron Lett.* **38,** 6989–6992 (1997).